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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,488	01/15/2004	David G. Gorenstein	UTMB:1019	5963

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/758,488	GORENSTEIN ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-12 and 14-96* is/are pending in the application.

4a) Of the above claim(s) *18-36 and 38-96* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-12,14-17 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Status of application

Claims 1-4, 6-12 and 14-96 are pending. Claims 1-4, 6-12, 14-17 and 37 are examined on the merits.

This application contains claims 18-36 and 38-96 drawn to an invention nonelected with traverse in the reply filed on December 21, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to arguments: Claim Rejections - 35 USC § 112

Claims 1-4, 6-12, 14-17 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained for the reasons set forth in rejection of claim 5 in the office action mailed March 16, 2006.

Applicant notes that claim 5 has been canceled, however, the subject matter of this claim has been incorporated into claims 1 and 37 and they are indefinite for the reasons previously applied to claim 5. Specifically, claims 1 and 37 recite a thioaptamer wherein the backbone comprises one or more α-thio modified nucleotide triphosphates.

Applicant might be intending to recite how the thio-phosphate is incorporated into an oligomer, but as the claim is read now it recites the presence of a triphosphate at some point within the nucleotide backbone. While nucleotide triphosphates might be used in the synthesis of oligomers, the normal nucleic acid backbone comprises single phosphates, not triphosphates. It is unknown if an oligomer comprising an internal triphosphate, producing a triphosphate ester linkage, is even possible. The only way that the examiner is aware of to incorporate a nucleotide triphosphate at an end of an oligomer is by transcription with T7 RNA polymerase. Claims 2-17 are indefinite for the same reasons due to their dependence from claim 1.

In the interests of compact prosecution this limitation has been interpreted as reciting thioaptamers comprising an α-thio modified nucleotide triphosphate at the 5' end of the oligomer.

Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. This rejection is maintained for the reasons set forth in the office action mailed March 16, 2006.

Applicant traverses the rejection of claim 37 by arguing that Opalinska teaches that some oligonucleotides can escape from vesicles and enter the cytoplasm and nucleus and that Opalinska further teaches that nucleic acid drugs are undergoing clinical trials and one nucleic acid drug has been approved to treat viral infections of the eye. Based on this, applicant concludes that Opalinska supports the knowledge of the skilled artisan in the area of nucleic acid drugs. This argument is not persuasive

because the teachings of Opalinska support the position that delivery of nucleic acids is unpredictable. The portion cited by the examiner and the further teaching quoted by applicant actually supports the position that delivery of nucleic acids for therapeutic purposes is unpredictable because whether a nucleic acid can escape the vesicles and enter the cytoplasm is a matter of chance. The skilled artisan would not know if any particular nucleic acid would enter the cytoplasm and would not know if enough would enter the cytoplasm to result in a therapeutic effect. The examiner acknowledges that some nucleic acids have proceeded to clinical trials or have been approved for drug use, but the basis for the rejection is in part based on the lack of a demonstrated therapeutic effect for the particular claimed oligonucleotides and the ability of other nucleic acids to act therapeutically does not lead the skilled artisan to recognize the instantly claimed nucleotides to act as a therapeutic.

Applicant further argues that based on the skill in the art and the teachings of the MPEP the claims fully comply with the enablement requirement and further argues that the present application does provide working examples based on work actually performed. The examiner agrees that a lack of working examples will not by itself render an invention non-enabled and that examples are not necessary if the disclosure otherwise enables one skilled in the art to practice the invention, however as set forth in the rejection, the disclosure does not otherwise allow the skilled artisan to practice the invention as it relates to a therapeutic compound. The examiner agrees that the specification provides working examples and guidance for making, isolating and characterizing thioaptamers, but the examples in the specification describe use of

thioaptamers in cells, not use of thioaptamers in vivo for therapeutic uses and therefore do not describe the full range of use of thioaptamers implied by the presence of the term "pharmaceutical" in the preamble.

This rejection may be overcome by removing the word "pharmaceutical" from the preamble of this claim.

Claim Rejections - 35 USC § 102

Claims 1-3, 6, 7, 9-12, 14-17 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Parrish et al. (Molecular Cell 2000, of record). This rejection is maintained for the reasons set forth in the office action mailed March 16, 2006.

Applicant traverses the rejection over Parrish et al. by arguing that Parrish does not teach all elements of the invention either explicitly or implicitly, arguing that Parrish does not teach a partially thio-modified thioaptamer that mediates gene silencing. This argument is not persuasive because Parrish does teach partially modified RNAs meeting the definition provided in the instant specification that a thioaptamer is a siRNA, an antisense oligonucleotide or a ribozyme. Parrish et al. disclose double stranded RNAs that induce RNA interference and comprise thiophosphates. Since one of the nucleotides is replaced with phosphorothioate linkages, these RNAs are partially thio-modified. The RNAs disclosed by Parrish et al. would necessarily be cleaved to siRNAs by the action of DICER. The RNAs disclosed by Parrish et al. are produced through T7 RNA polymerase transcription as described on page 1085, first column and would therefore have α-thio triphosphates at the 5' end as recited in the amended claims.

Applicant further traverses the rejection by alleging Parrish to be non-enabling. Applicant argues that Parrish does not teach a thioaptamer with perfect or imperfect complementarity match to a target gene and argues that Parrish teaches sequence and motifs to be unimportant. The portion of the reference pointed to by applicant is actually stating that induction of RNAi does not require any particular sequence or motif (analogous to, for instance, a promoter sequence that indicates a transcription start site), not that target complementarity is unimportant. It was well-known in the art at the time of the Parrish reference that RNAi directs gene silencing through complementarity to the target and the RNAs of Parrish et al. have such complementarity. Applicant further argues that Parrish indicates short dsRNAs may have no role in RNAi. It is noted that the citation pointed to by applicant is not a conclusion reached by Parrish, but a report on the conjectures of another author. However, even if Parrish did have this opinion, this does not change the inherent disclosure of Parrish of short RNAs, it is not required that the prior art recognize an inherent feature. Finally, applicant argues that the sequences listed in figure 1 of Parrish contain 3 of the 4 nucleotides. This argument cannot be address because the relevance is not understood; the instant claims have no limitations requiring 4 different nucleotides.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6-12, 14-17 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parrish et al. as applied to claims 1-3, 6, 7, 9-12, 14-17 and 37 above, and further in view of Elbashir et al. (EMBO Journal 2001, vol. 20, pages 6877-6888).

Claims 1-3, 6, 7, 9-12, 14-17 and 37 are directed to thioaptamers that mediate gene silencing. The thioaptamer may comprise a 3' OH group, may be composed of ribonucleotides, may comprise a double stranded RNA fully complementary to a target that silences the gene by mRNA cleavage and may be 15-22 or 21-25 nucleotides in length. The thioaptamer may be part of a RISC complex, may be produced by a DICER complex and may be a siRNA. Claims 4 and 8 limit claim 1 by reciting that the thioaptamer comprises deoxyribonucleotides and can comprise an imperfect complementarity to a target gene.

Parrish et al. teach double stranded RNAs comprising phosphorothioate linkages that are complementary to and inhibit the *unc-22* gene of *C. elegans* by RNA interference. Parrish et al. teach in a separate embodiment the modification of the RNAs by substitution with deoxynucleotides. These RNAs are necessarily cleaved to produce RNAs 21-25 nucleotides long as described in the 102 rejection over Parrish et al. in the office action mailed March 16, 2006. The RNAs taught by Parrish et al. are produced through T7 RNA polymerase transcription as described on page 1085, first column and would therefore have α-thio triphosphates at the 5' end as recited in the

amended claims. Parrish et al. do not teach siRNAs comprising both phosphorothioates and deoxynucleotides or RNAs that are imperfectly complementary to a target gene.

Elbashir et al. teach short RNAs 21 nucleotides in length that inhibit gene expression. Elbashir et al. teach (see page 6881, second column) that RNAs substituted at the 3' terminus with deoxynucleotides efficiently mediate RNA interference and suggest that such substitutions may also protect the RNA from ribonucleases. At page 6884 Elbashir et al. also teach that RNAs with imperfect complementarity function to mediate RNA interference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Parrish and Elbashir to make dsRNAs with both phosphorothioates and deoxynucleotides and to use these siRNAs to downregulate gene expression, even in the presence of mismatches. Elbashir et al. provide a motivation and reasonable expectation of success in making siRNAs comprising deoxynucleotides by teaching that such substitutions reduce cost of synthesis and may increase nuclease resistance and function to mediate RNAi. The skilled artisan would be motivated to incorporate phosphorothioates into a nucleic acid by recognizing that such substitutions increase nuclease resistance and Parrish provides a reasonable expectation of success in making such siRNAs by demonstrating such modifications do not affect RNAi. Based on the teachings of Elbashir et al. that siRNAs comprising mismatches will mediate RNAi, the person of ordinary skill in the art would be motivated to target genes known to have polymorphisms in order to make an siRNA that will function against different gene polymorphs. Thus, the invention of

claims 1-4, 6-12, 14-17 and 37 would have been obvious, as a whole, at the time of invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
October 25, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER